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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
BASKAR, PADMAVATHI

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 04/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/034,500	JACOBS ET AL.	
	Examin r	Art Unit	
	Padmavathi v Baskar	1645	

-- The MAILING DATE of this communication appears on th cov r sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15 and 18-38* is/are pending in the application.

4a) Of the above claim(s) *1-8,11,12,14,15,22-33,36 and 37* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *9,10,13,18-21,34 and 35* is/are rejected.

7)☒ Claim(s) *38* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's amendment filed on 3/26/2003, paper # 10 is acknowledged. Claims 9, 11, 13,18 and 38 have been amended. Claims 1-15, 18-38 are pending in the application.

Priority

2. Receipt is acknowledged of papers submitted (the certified copy of EPO 00204660 filed on12/20/2000) under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file. Accordingly priority is accorded as of 12/20/2000 for the elected claims.

Information Disclosure Statement

3. Information Disclosure Statement filed on 12/9/02 (Paper # 5) is acknowledged and a signed copy is attached to this Office action.

Specification - Informalities

4. This application is informal in the arrangement of the specification. Applicant attention is directed to MPEP 608.01(a). For Example: After Summary of the Invention.
Brief Description of the Drawing should be recited. Applicant is advised to amend the specification, page 26 " Legends of Figures" to read as Brief Description of the Drawings
Claims should begin with "I claim" or "'We claim" or "What is claimed is".
The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code, see in particular at least pages 3 and 9. Applicant is required to delete the embedded hyperlink and/or other form of browser- executable code. See MPEP § 608.01. The worldwide web address can be readily changed with rapidly changing technology

and therefore, may not be available to the public. Therefore, applicant is advised to amend the specification.

Sequence Requirements

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. 1.821-1.825 for the reason(s) set forth below:

The specification on page 12 and 25 discloses a number sequences related to primers and proteins. However, these sequences are not in compliance with the sequence rules.

6. Full compliance with the sequence rules is required in response to this office action. A complete response to this office action should include compliance with the sequence rules. Failure to fully comply with these requirements in the time period set forth in this office action will be held non-responsive.

Election/Restriction

7. Applicant's election of Group II, Claims 9-15, 18-21 and 34-38 with respect to SEQ.ID.NO: 2 in Paper No. 10 is acknowledged. The traversal is on the ground(s) that the proteins SEQ.ID.NO: 2 and 4 are related as being proteins of L. intracellularis as well as being few in number and search and examination would not be an undue burden. This is not found persuasive.

The specification, page 2, lines 19 and 20 recite that the amino acid sequences of the 37kD and 50kD proteins are presented in sequence identifiers as SEQ.ID.NO: 2 and 4 respectively. These two proteins appear to be novel outer membranes proteins and unique in their structure as 37kD protein comprises 218 amino acids (SEQ.ID.NO: 2) and 50kD protein

contains 475 amino acids (SEQ.ID.NO: 4). Therefore, these two proteins are considered as distinct inventions and are properly restricted under 35 U.S.C. 121.

Concerning the burden of search is merely one indication of the burdensome nature of the search involved. The protein database searches required by each of the sequences and the literature searches for each of the sequences, both of which are particularly relevant in this art, are not co-extensive and are much more important in evaluating the burden of search. For example, search and examination issues for different proteins and vaccines are different. Clearly different searches and issues are involved in the examination of each group.

The requirement is still deemed proper and is therefore made FINAL.

8. Claims 9, 10, 18-21, 34-35 and 38 are under examination with respect to SEQ.ID.NO: 2.

Applicant is advised to amend the elected invention, Claims 9, 10, 18-21, 34-35 and 38 to restrict to SEQ.ID.NO: 2. Outer membrane protein 19/21kD and SEQ.ID.NO: 4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected subject matter, said election made in Paper # 10

9. Claims 1-8, 11-15, 22-33 and 36-37 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected inventions, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in Paper No. 10.

Claim objection

10. Claim 38 is objected to under 37 CFR 1.75(c) as being in improper multiple dependent form. Applicant is advised to amend the claim.

However, in order to advance the prosecution, the examiner is considering claim 38 as if it depends from the elected claim 9 for examination purposes.

Claim Rej ctions - 35 USC 101

11. 35 U.S.C. 101 reads as Follows

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefore, subject to the conditions and requirements of this title.

12. Claims 9 –10 and 34-35 rejected less than 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed invention is drawn to a Lawsonia intracellularis protein and read on product of nature. Products of nature are not patentable because they do not reflect the "hand of man" in the production of the product or manufacturing process. Diamond v. Chakrabarty, 206 USPQ 193 (1980). It is suggested to include the terminology " an isolated protein" to overcome the rejection.

Claim Rejections - 35 U.S. C. 112, first paragraph

13. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

14. Claims 9-10, 18-21, 34, 35 and 38 are rejected under 35 U.5.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is referred to the interim guidelines on written description published June 15, 1998 in the Federal Register at Volume 63, Number 114, pp 32639-32645 (also available at www.uspto.gov). This is a written description rejection.

The claims are drawn to Lawsonia intracellularis protein having homology, 70%, 80%, 90% and 95% to amino acid sequence SEQ.ID.NO: 2 (the examiner is considering these as variants) and immunogenic fragments of said protein.

The examiner is considering claim 38 as if it depends from the elected claim 9 for examination purposes.

The specification broadly describes as part of the invention, an isolated protein of SEQ ID NO: 2, which is a " 37kD outer membrane protein "on page 2, lines 19 and 20. The specification also teaches on page 22 that 37 kD protein has been amplified and cloned as a 656 bp product. However, the specification does not teach Lawsonia intracellularis protein having homology to, 70%, 80%, 90% and 95% amino acid sequences of SEQ.ID.NO: 2 or fragments of said protein.

The actual biological function of the protein represented as SEQ ID NO: 2 and as a vaccine composition is not set forth in this specification. Applicants broadly describe the invention as embracing any deletion by use of language in which a specified percent of amino acids can be changed in the protein. USPQ2d 1111, makes clear that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed." (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that (he or she] invented what is claimed." (See Vas-Cath at page 1116).

Thus, an isolated Lawsonia 37kD protein comprising of SEQ ID NO: 2 meets the written description provision of 35 U.S.C. 112, first paragraph for the reasons set forth below.

The specification fails to teach a protein sequence of 70%, 80%, 90% and 95% of homology with SEQ ID NO: 2 and it is noted that the claimed variants do not exist as an

invention independent of their function in encoding a protein. The actual structure or other relevant identifying characteristics of each protein (i.e. homolog) having the claimed properties of the 37 kD protein can only be determined empirically by actually making every nucleic acid that encodes the recited variability (i.e. the instant 70%, 80%, 90% and 95% identity) and testing each to determine whether such a protein having the particularly disclosed properties of an 37 kD protein. For example, if there is a well-established correlation between structure and function in the art, one skilled in the art will be able to reasonable predict the complete structure of the claimed invention from its function. This specification does not teach such, and the art is devoid of this correlation for SEQ ID NO: 2, 37kD protein with undetermined function. There is no written description support for protein sequence of 70%, 80%, 90% and 95% of homology with SEQ ID NO: 2 as claimed.

The 37kD protein comprising of SEQ ID NO: 2 is uncharacterized by this specification and is not asserted to belong to any known family of proteins. The specification fails to teach the structure or relevant identifying characteristics of a representative number of SEQ.ID.NO: 2 (37 kD protein) variants/fragments, sufficient to allow one skilled in the art to determine that the inventor had possession of the invention as claimed. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method for isolating it. See Fiers v. Revel, 25 U5PQ2d 1601, 1606 (CAFC 1993) and Amgen Inc V Chuaai Pharmaceutical Co Ltd., 18 U5PQ2d 1016. One cannot describe what one has not conceived. See Fiddes v. Baird, 30 U5PQ2d 1481, 1483. In Fiddes v. Baird, claims directed to mammalian FGF's were found unpatentable due to lack of written description for the broad class.

15. Claims 9-10 and 34-35 are also rejected under 35 U.5.C. 112, first paragraph, because the specification, while being enabling for an isolated Lawsonia intracellular protein comprising

SEQ ID NO: 2, the specification does not reasonably provide enablement for a protein with a sequence homology 70%, 80%, 90% and 95% to SEQ ID NO: 2. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims since there is no written description support for the claimed invention.

These claims are not enabled for the following reasons. The written description is limited to only SEQ ID NO: 2 which is a 37kD protein comprising of SEQ ID NO: 2 and described as an outer membrane protein of *L. intracellularis.* The specification fails to indicate that a protein with a sequence homology 70%, 80%, 90% and 95% to SEQ ID NO: 2 or antigenic fragments thereof and fails to teach that the claimed antigenic fragments are detected by immune sera and further lacks any description of any such fragments. The specification is not enabled for any variant /fragment of a protein comprising SEQ ID NO: 2 or antigen fragment thereof because 1) the specification fails to teach a protein comprising 70%, 80%, 90% and 95% of homology with SEQ ID NO: 2 or fragment thereof is able to function by binding immune sera; 2) the specification fails to teach how to make and use variants/fragments thereof that have an unknown and uncharacterized function; 3) the specification fails to teach what are the critical protein residues that can be modified and still achieve a protein with functional activity 4) the art teaches that proteins with replacement of single amino acid residues may lead to both structural and functional changes in biological activity and immunological recognition, one skilled in the art would have reason to doubt the validity and functionality of the function of such antigen variants or antigenic fragments of SEQ ID NO:2, and 5) applicants have not displayed a nexus between the structure and function of the claimed fragments/variants. As to points 1)- 5), the specification fails to provide a written description of any protein variants/fragments of a bacterial protein sequence of SEQ ID N0: 2. The specification fails to teach the critical protein residues

involved in the function of the protein SEQ ID NO: 2, such that the skilled artisan is provided no guidance to test, screen or make variants/fragments of the protein comprising SEQ ID NO: 2. The specification fails to teach to what extent one could alter SEQ ID NO: 2 and still present the sequence as a functional protein. Moreover, protein chemistry is probably one of the most unpredictable areas of biotechnology and the art teaches that the significance of any particular amino acid and sequences for different aspects of biological activity can not be predicted a priori and must be determined empirically on a case by case basis (Rudinger et al, in "PEPTIDE HORMONES", edited by Parsons, J.A., University Park Press, June 1976, page 6). The art specifically teaches that even a single amino acid change in a protein leads to unpredictable changes in the biological activity of the protein. For example, replacement of a single lysine residue at position 118 of the acidic fibroblast growth factor by glutamic acid led to a substantial loss of heparin binding, receptor binding, and biological-activity of the protein (Burgess et al., The Journal of Cell Biology, 111:2129-2138, 1990). In transforming growth factor alpha, replacement of aspartic acid at position 47 with alanine, or asparagine did not affect biological activity while replacement with serine or glutamic acid sharply reduced the biologic activity of the mitogen (Lazar et al., Molecular and Cellular Biology, 8(3): 1247-1252, 1988). These references demonstrate that even a single amino acid substitution or what appears to be an inconsequential chemical modification, will often dramatically affect the biological activity of a protein. Proteins with replacement of a single amino acid residue may lead to both structural and functional changes in biological activity and immunological recognition. For example, Jobling et al. (Mol. Microbiol, 1991, 5(7): 1755-67 teaches a panel of single amino acid substitutions by oligonucleotide directed mutagenesis which products proteins that differ in native conformation, immunological recognition, binding and toxicity, thus exemplifying the importance of structural components to both biological function and immunological recognition.

Applicants have not taught which residues of SEQ ID NO: 2 can be varied and still achieve a protein that is functional. Since, the specification lacks a written description of any variant or fragment of SEQ ID NO: 2, it is not enabled for this language because it fails to enable the skilled artisan to envision the detailed chemical structure of the claimed variants or fragments of SEQ.ID.NO: 2 as well as how to use the claimed protein or antigenic fragments of SEQ ID NO: 2. The skilled artisan would be forced into undue experimentation to make and use the instantly claimed invention.

16. Claims 18-21 rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The state of the prior art indicates little is known about the humoral and, especially, cell-mediated immune response in pigs exposed to Lawsonia intracellularis. Pathogenesis of L. intracellularis has not been well investigated; however, organisms cultured in vitro have been used successfully to reproduce the disease in vivo. This bacterium has a tropism for intestinal epithelial cells, and the major pathological consequence of infection is hyperplasia of infected epithelial cells. The specific bacterial determinants which confer pathogenicity and cause these distinctive pathological effects are not known (see McCluskey et al, Infect Immun 2002 Jun; 70(6): 2899-907) Bacterial attachment and entry occur via the apical surface of immature epithelial cells in a process which appears to require a specific bacterial ligand-receptor interaction and once inside the cell, the bacteria escape from the vacuolar compartment into the cytoplasm, where they multiply and spread from cell to cell following cell division. At present, the determinants used by L. intracellularis to enter the cell, escape the vacuole, multiply intracytoplasmically, and modulate host cell function are not known. Therefore, the claimed outer-membrane protein induces an effective immune response such that it can be used, as a

vaccine composition is not predictable in this underdeveloped art. The specification, however, provides no working examples demonstrating (i.e., guidance) enablement for any *in vivo* uses of the claimed protein.

The specification fails to teach how to formulate and use the claimed vaccine. The term "vaccine" encompasses the ability of the specific antigen to induce any immune response or protective immunity to Lawsonia infection or disease induction. This demonstration is required for the skilled artisan to be able to use the claimed vaccine for their intended purpose of preventing intracellularis infection. Without this demonstration, the skilled artisan would not be able to reasonably predict the outcome of the administration of the claimed vaccines i.e. would not be able to accurately predict if protective immunity has been induced.

The induction of specific immunity to the outer membrane proteins appears to be at the earliest stages of identifying the antigens. Thus, prevention of infection using uncharacterized bacterial antigens must be considered highly unpredictable, requiring a specific demonstration of efficacy on a case-by-case basis. Absent such demonstration, the invention would require undue experimentation to practice as claimed.

Vaccines by definition trigger an immunoprotective response in the host vaccinated and mere antigenic response is insufficient to provide for enablement of vaccines. This specification fails to teach any immune response generated by means of the claimed vaccine. It is well recognized in the vaccine art, that it is unclear whether an antigen(s) derived from a pathogen will elicit protective immunity. Ellis, R.W. (Chapter 29 of "VACCINES" [Plotkin, 5.A. et al. (eds) published by W. B.Saunders company (Philadelphia) in 1988, especially page 571, 2nd full paragraph] exemplifies this problem in the recitation that "The key to the problem (of vaccine development) is the identification of that protein component of a virus or microbial pathogen that itself can elicit the production of protective antibodies.... and thus protect the host against attack

by the pathogen". The specification fails to teach the claimed protein alone or in combination with other antigens does in fact confer protection from infection, as is requisite of a vaccine composition. While the specification teaches a putative 37 kD protein the art does not recognize the claimed protein as therapeutic vaccines capable of conferring protection against L.intracellularis challenge in an immunized host.

Status of Claims

17. No claims are allowed.

18. An isolated Lawsonia intracellularis protein comprising the amino acid sequence SEQ.ID.NO: 2 is free of prior art.

19. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Padma Baskar whose telephone number is (703) 308-8886. The examiner can normally be reached on Monday through Friday from 6:30 AM to 4 PM EST

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on (703) 308-3909. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Padma Baskar Ph.D

4/13/03

Patricia A. Duffy
PATRICIA A. DUFFY
PRIMARY EXAMINER